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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/662,438	09/16/2003	Neil Wolfman	08702.0128-00000	2654

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/662,438	WOLFMAN ET AL.	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *16-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/04, 3/04, 4/05,* 6/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application is a non-provisional of provisional application of 60/486,863 of 7/10/2003, 60/439,164 of 1/9/2003 and 60/411,133 of 9/16/2002.

The preliminary amendment filed on 9/6/2003 is acknowledged. Claims 1-21 are at issue and are present for examination.

Applicant's election with traverse of Group I, Claims 1-15, drawn to an agent or a peptide that modulates metalloprotease activity, which mediates activation of latent myostatin, by cleavage and invention (E) peptide of SEQ ID NO: 23 in the response filed on 4/18/2006 is acknowledged.

Applicant's traverse is on the ground(s) that the examiner has not established that a serious burden would be imposed on the Patent Office if inventions (A)-(E) i.e. (A). Peptide of SEQ ID No: 11, (B). Peptide of SEQ ID No: 14, (C). Peptide of SEQ ID No: 17, (D). Peptide of SEQ ID No: 20 and (E). Peptide of SEQ ID No: 23 were searched and examined together because each of the groups are drawn to structurally related peptide of decreasing size having amino acid sequences, are portions of myostatin propeptide. This is not persuasive because contrary to applicants arguments, a search for each of the sequences would not be done solely by searching electronic sequence databases as such databases seldom provide extensive coverage of all variants which are known or have been made of a single protein such that word searching for each variant is required. Such searching would likely be different for each variant as each change may have distinct effects. Furthermore, even sequence searching of the five different variants would be a substantial burden on the office as each sequence has to be examined individually to

determine if it includes each claimed variant as a search could not be done just for (A) because while references teaching any of (A)-(D) would anticipate (E), but search of only (A) might miss the prior art of (E) because (E) is so small. Similarly a search of only (E) could not be done either as reference teaching (E) would not necessarily also anticipate or make obvious (A)-(D). Therefore, searching all the peptides (A) – (E) and variants and novelty and non-obviousness of each variant would have to be addressed individually creating a large burden on the office. In addition, the independence and distinctness of each of the peptide sequence is discussed in detail in the previous office action i.e. each of the peptide sequence is chemically, structurally and functionally independent and distinct (i.e. structurally and functionally can be similar but not same).

"*For purposes of the initial requirement, a serious burden on the examiner may be prima facie shown if the examiner shows by appropriate explanation either separate classification, separate status in the art, or a different field of search as defined in MPEP 808.02.*" (see MPEP 803).

The requirement is still deemed proper and is therefore made FINAL.

Claims 3 and 16-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in communication filed on 8/02/2005.

Claims 1-2 and 4-15 are under consideration and are being examined herein.

Priority

Acknowledgement is made of applicants claim for US provisional application of 60/486,863 of 7/10/2003, 60/439,164 of 1/9/2003 and 60/411,133 of 9/16/2002.

Claim Objections

Claims 5-15 are objected to because of the recitation "An agent ---", which refers to a previous claim. "An agent ---" should be changed to "The agent ----". Appropriate correction is required.

Claims 4 and 11 are objected to as encompassing non-elected subject matter. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-2 and 4-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite in the recitation of the "a derivative of said peptide" which is confusing. What does this encompass? Accordingly, claims 1-2 and 4-15 are rejected, as they are dependent on claim 1.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-10, 13-15 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to an agent that modulates metalloprotease-mediated activation of latent myostatin, said agent comprising a peptide, wherein said peptide comprises a peptide portion of a myostatin polypeptide, or a derivative of said peptide portion, wherein the derivative of the peptide portion of the myostatin polypeptide comprises a peptide having a mutation of a cleavage site for the metalloprotease. Claim 2 recites that said agent reduces or inhibits metalloprotease-mediated activation of latent myostatin. Claims 5-7 recite that said agent is operably linked to a second molecule, which comprises a detectable label that is a heterologous polypeptide and claim 8 recites that the heterologous polypeptide stabilizes the peptide. Claim 9 recites that the said heterologous polypeptide comprises an Fc domain of an antibody and claim 10 recites that the said agent is a fusion protein. Claim 13-15 recite that the said metalloproteases are BMP/TLD family member proteins. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A

representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the structure of only several representative species of such agents (peptides). Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the identifying characteristics of the agent (peptide), which inhibits cleavage of latent myostatin. Given this lack of description of representative species encompassed by the genus of peptide used in the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 1-2, 5-10, and 13-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an agent of SEQ ID NO: 23 that modulates metalloprotease-mediated activation of latent myostatin, does not reasonably provide enablement for any agent that modulates metalloprotease-mediated activation of latent myostatin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-2, 5-10, and 13-15 are so broad as to encompass any peptide agent that modulates metalloprotease-mediated activation of latent myostatin. Claim 2 recites that said agent reduces or inhibits metalloprotease-mediated activation of latent myostatin. Claims 5-7 recite that said agent is operably linked to a second molecule, which comprises a detectable label that is a heterologous polypeptide and claim 8 recites that the heterologous polypeptide stabilizes the agent, which is a peptide. Claim 9 recites that the said heterologous polypeptide comprises an

Fc domain of an antibody and claim 10 recites that the said agent is a fusion protein. Claim 13-15 recite that the said metalloproteases are BMP/TLD family member proteins. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of peptides broadly encompassed by the claims. Since the amino acid sequence of a peptide or a protein determines its structural and functional properties, predictability of which changes can be tolerated in a peptide or protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the peptide or protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the amino acid sequences of only a few peptides.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions.

The specification does not support the broad scope of the claims which encompass any peptide agent that modulates metalloprotease-mediated activation of latent myostatin because the specification does **not** establish: (A) regions of the peptide agent or protein structure which may be modified without effecting its activity; (B) the general tolerance of peptides to modification

and extent of such tolerance; (C) a rational and predictable scheme for modifying any peptides or protein residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any peptide agent that modulates metalloprotease-mediated activation of latent myostatin. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any peptide agent that modulates metalloprotease-mediated activation of latent myostatin having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, and 5-10 and 13-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Wolfman et al. (WO02/068650, publication 9/6/2002, claim priority of 60/267,509 of 8/2/2001, see IDS). Wolfman et al. disclose a propeptide which is 88.2% identical to SEQ ID

NO: 23 of the instant application, which modulates myostatin activation (GDF-8) by reducing the cleavage of pro-myostatin, wherein the propeptide has mutation at the cleavage site of the pro-myostatin (GDF-8) results in increase of half life of pro-myostatin i.e. decrease the activity of active myostatin (cleaved). Wolfman et al. also disclose that the propeptide further comprises a stabilizer portion fused to propeptide resulting in a fusion protein, wherein the stabilizer portion comprises an Fc region of an antibody, which stabilize the propeptide. Because the peptide inhibits pro-myostatin protein cleavage by inhibiting the protease activity by binding to the protease, therefore the peptide of Wolfman et al. would inherently inhibit recited protease (BMP-1/TLL/TLD family of protease), of the instant application. Therefore, Wolfman et al. anticipates claims 1-2 and 5-10 and 13-15 of the instant application.

Conclusion

Status of the claims:

Claims 1-2, and 4-15 are pending.

Claims 1-2, and 4-15 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Iqbal Chowdhury, PhD, Patent Examiner

Art Unit 1652 (Recombinant Enzymes)
US Patent and Trademark Office
Rm. REM 2B69, Mail Box. 2C70
Ph. (571)-272-8137, Fax. (571)-273-8137

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REBECCA E. PRUTY
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